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Dated: May 9, 2000.

John L. Williams,

Director, Procurement and Grants Office, Centers for Disease Control and Prevention (CDC).

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1219]

Biological Products; Bacterial Vaccines and Related Biological Products; Implementation of Efficacy Review; Proposed Order

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed order to accept the conclusions and recommendations of advisory review panels concerning the safety, effectiveness, and labeling of certain bacterial vaccines and related biological products that were previously classified into Category IIIA (remaining on the market pending further studies in support of effectiveness). On the basis of the advisory review panel findings, FDA is proposing to reclassify the relevant Category IIIA products into Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded). This action is being taken under the reclassification procedures.

DATES: Submit written comments on this proposed order and the reclassification of products should be submitted by August 13, 2000. Data and information submitted to FDA in connection with these reclassified products will be made publicly available after June 14, 2000. Comments concerning confidentiality should be received by FDA before June 14, 2000.

ADDRESSES: Submit written comments on the proposed order to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Comments may also be submitted electronically at www.fda.gov/ohrms/dockets. Copies of the reports from the Vaccines and Related Biological Products Advisory Committee (April 1984) and the Panel on Review of Allergenic Extracts (December 1983) can be obtained from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Requests for copies that are accompanied by a self-addressed adhesive label will assist that office in processing your requests. The documents may also be obtained by mail either by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800 or by submitting a request electronically at www.CBER_INFO@CBER.FDA.GOV, or by fax by calling the FAX Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT: Steven Falter, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6343.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Review Procedures (21 CFR 601.25)

On July 1, 1972, responsibility for regulating biological products under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) was transferred from the National Institutes of Health to FDA (37 FR 12865, June 29, 1972). Section 351 of the PHS Act provides statutory authority to license biological products. In 1973, FDA established a procedure to review the safety, effectiveness, and labeling of all biological products licensed prior to July 1, 1972 (38 FR 4319, February 13, 1973). This process was eventually codified in § 601.25 (21 CFR 601.25) (38 FR 32048 at 32052, November 20, 1973). Under § 601.25, the Commissioner of Food and Drugs assigned responsibility for the initial review of all biological products licensed prior to 1972 to nine independent advisory review panels. These panels consisted of qualified nonFDA experts in order to ensure public confidence in, and objectivity of the reviews. Each of the advisory review panels was assigned to review a specific category of biological products.

In the **Federal Register** of June 19, 1974 (39 FR 21176), FDA eliminated three previously planned panels (The Panel on Review of In Vitro Diagnostic Reagents; The Panel on Review of Immune Serums, Antitoxins, and Antivenins; and the Panel on Review of Miscellaneous Biological Products) and reassigned the review of the biological products originally intended for review by these three panels to the remaining six advisory review panels: The Panel on Review of Bacterial Vaccines and Toxoids with Standards of Potency, The Panel on Review of Bacterial Vaccines and Bacterial Antigens with "no U.S. Standards of Potency," the Panel on Review of Skin Test Antigens, The Panel on Review of Allergenic Extracts, The Panel on Review of Viral and Rickettsial Vaccines, and the Panel on Review of Blood and Blood Derivatives. The advisory review panels for bacterial vaccines and bacterial antigens with "no U.S. standard of potency," bacterial vaccines and toxoids with standards of potency, and skin test antigens reviewed the products that are the subject of this notice.

Under the review and classification procedures specified in § 601.25, each advisory review panel was charged with preparing a report to the agency that: (1) Evaluated the safety and effectiveness of the biological product; (2) reviewed the labeling of the biological product; and (3) advised FDA on which biological products under review were safe, effective, and not misbranded. Each advisory review panel report was to include a statement classifying the products into Category I, Category II, or Category III. Category I designated those biological products determined to be safe, effective, and not misbranded. Category II designated those biological products determined to be unsafe, ineffective or misbranded. Category III designated those biological products that did not fall within either Category I or Category II because of insufficient data and for which further testing was therefore required. Category III products were assigned to one of two subcategories. Category IIIA products were those that would be permitted to remain on the market pending the completion of further studies. Category IIIB products were those for which the panel report recommended license revocation on the basis of the panel's assessment of potential risks and benefits.

After reviewing the conclusions and recommendations of the panels, FDA would publish in the **Federal Register** a proposed order containing: (1) A statement designating the biological products reviewed into Categories I, II, IIIA or IIIB; (2) a description of the testing necessary for Category IIIA biological products; and (3) the complete panel report. Under the proposed order, FDA would revoke the licenses of those products designated into Category II and Category IIIB. After reviewing public comments, FDA would publish a final order on the matters covered in the proposed order.

B. Section 601.25 and Products Subject to This Proposed Order

1. The Panels on Review of Skin Test Antigens and Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency"

In the **Federal Registers** of September 30, 1977 (42 FR 52674), and November 8, 1977 (42 FR 58266), FDA published proposals for the implementation of the efficacy reviews for skin test antigens and bacterial vaccines and antigens with "no U.S. standard of potency," respectively. These proposals were in response to the reports of The Panel on Review of Skin Test Antigens, and the Panel on Review of Bacterial Vaccines and Antigens with "no U.S. standard of potency," and contained each Panel's findings and recommendations to designate each of the products reviewed into Categories I, II, IIIA or IIIB. In these proposed orders, FDA agreed with each Panel's findings and recommendations, and in accordance with §§ 601.5(b) (21 CFR 601.5(b)) and 601.25(f)(3), notified manufacturers of those products identified for classification into Category II or Category IIIB of the agency's intent to publish a notice of an opportunity for hearing to revoke the licenses for these products. Additionally, in accordance with § 601.25(f)(3), FDA proposed that those products identified for classification into Category IIIA remain on the market and that their licenses remain in effect on an interim basis pending completion of scientifically sound studies to demonstrate efficacy in humans. In the **Federal Registers** of October 28, 1977 (42 FR 56800), and December 9, 1977 (42 FR 62162), under 21 CFR 12.21(b), FDA published notices of opportunity to request hearings, submit additional data, and comment on the proposed revocation of licenses for certain skin test antigens and bacterial vaccines and antigens with "no U.S. standard of potency," respectively. Through these FR notices, manufacturers of skin test antigens and bacterial vaccines and antigens with "no U.S. standard of potency" previously identified for classification into Category II or Category IIIB were offered an opportunity for a hearing on the proposed revocation of existing licenses for products placed in Category II or IIIB.

The manufacturers of skin test antigens and bacterial vaccines and antigens with "no U.S. standard of potency," whose products were identified as Category II or Category IIIB either: (1) Did not request a hearing, (2) requested a hearing but submitted no data, (3) requested a hearing and submitted additional data that justified reclassification of products without the need for the requested hearing, or (4) requested that their product licenses be revoked. Therefore, FDA published in the **Federal Register** of October 27, 1978 (43 FR 50247), a notice reclassifying one bacterial vaccine with "no U.S. standard of potency" from Category IIIB into Category IIIA, and revoking the product licenses for the remaining bacterial vaccines and bacterial antigens with "no U.S. standard of potency" classified in Category II or Category IIIB. In the **Federal Register** of October 27, 1978, FDA also published a notice reclassifying certain skin test antigens from Category IIIB into Category IIIA, and revoking the product licenses for the remaining skin test antigens classified as Category IIIB (43 FR 50250).

2. The Panel on Review of Bacterial Vaccines and Toxoids with Standards of Potency

In the **Federal Register** of December 13, 1985 (50 FR 51002), FDA published a proposed rule containing the implementation of the efficacy review for bacterial vaccines and toxoids with standards of potency (hereinafter referred to as the December 1985 proposal). The December 1985 proposal was in response to the report of The Panel on Review of Bacterial Vaccines and Toxoids with Standards of Potency, and contained the Panel's findings and recommendations to designate each of the products reviewed into Categories I, II, IIIA or IIIB. In the December 1985 proposal, FDA: (1) Disagreed with the Panel's findings and recommendations to classify some products as Category IIIB, and reclassified these products into Category I, (2) agreed with the Panel's recommendations to classify the remaining products into Category II or Category IIIB, and (3) provided notice that licenses for several products recommended by the Panel for classification into Category IIIB and the license for the single product recommended for classification into Category II were voluntarily revoked at the request of the manufacturers prior to publication of the proposed order.

Subsequent to the Panel's review but prior to the publication of the December 1985 proposal, the regulations were revised and reclassification review procedures were established under § 601.26 (21 CFR 601.26) (47 FR 44062 at 44071, October 5, 1982). Therefore, the classification process for bacterial vaccines and toxoids with standards of potency will be completed in accordance with § 601.26 as described below.

II. Reclassification Procedures (Section 601.26)

A. The Reclassification Process

In 1982, FDA issued a regulation that established procedures to reclassify those products in Category IIIA into either Category I or Category II (47 FR 44062, October 5, 1982). This regulation was codified in § 601.26. According to § 601.26, Category IIIA products that would be reclassified included: (1) Products that an advisory panel had recommended be assigned to Category IIIA, (2) products that FDA had proposed to place in Category IIIA, or (3) products for which FDA had issued a final order reclassifying the products into Category IIIA. Under § 601.26, advisory review panels would review all Category IIIA products and make recommendations concerning each product's reclassification. During the advisory panel reclassification review process, interested persons were permitted to attend meetings, appear before the advisory review panels, and submit data to the panels for review. The advisory review panels would then submit a report to FDA that recommended the reclassification of each Category IIIA product into either Category I or II. After reviewing the conclusions and recommendations of the advisory panels, FDA would publish in the **Federal Register** a proposed order containing the following: (1) A statement designating the products as Category I or Category II, (2) a notice of availability of the full panel report, (3) a proposal to accept or reject the findings of the advisory review panels, and (4) a statement identifying those products that FDA proposes should be permitted to remain on the market because of a compelling medical need and no suitable alternative exists as described in § 601.26(d)(4).

B. Section 601.26 and the Products Subject to this Proposed Order

FDA assigned the reclassification review of bacterial vaccines and related biological products previously classified into Category IIIA by FDA based on the recommendations of the Panel on Review of Bacterial Vaccines and Antigens with "no U.S. Standard of Potency" and the Panel on Review of Skin Test Antigens to the Vaccines and Related Biological Products Advisory Committee (VRBPAC). FDA also assigned the reclassification review of vaccines and related biological products previously recommended for classification into Category IIIA by the Panel on Review of Bacterial Vaccines and Toxoids with Standards of Potency to the VRBPAC. In accordance with the

procedures specified above, FDA is notifying the public through this **Federal Register** notice of the agency's proposed reclassification of the Category IIIA products reviewed by the VRBPAC.

This proposed order contains notice of FDA's intent to revoke the licenses of certain vaccines and related biological products, listed below, that FDA proposes, based on VRBPAC recommendations, to reclassify from Category IIIA to Category II. The public may submit comments to FDA concerning this proposed order. After the end of the comment period, if FDA determines to go forward with the license revocation proceedings, the agency will publish a notice of opportunity for hearing (NOOH) on the revocation of the license of each product in Category II. After reviewing the comments on the proposed order, FDA will issue a final order on the matters covered in the proposed order. Depending upon whether a manufacturer requests a hearing on the revocation of its biologics license, FDA may consolidate the final order with license revocations.

III. Identification of Category IIIA Products Subject to Reclassification

A. Review and Reclassification Procedures, Bacterial Vaccines and Toxoids With Standards of Potency. (Bacterial Vaccines and Toxoids with Standards of Potency, Antitoxins, and Immune Globulins)

In the December 1985 proposal, FDA identified those products that were originally recommended for classification into Category IIIA and that were now subject to review by the VRBPAC under § 601.26.

Several bacterial vaccines and toxoids with standards of potency were classified into two categories based upon their use as a primary immunogen or as a booster. For example, a vaccine product could be assigned a Category IIIA designation for use as a primary immunogen but could be designated as Category I for booster use. The classifications were different because the potency tests for diphtheria and tetanus toxoids were found suitable for determining the acceptability of the toxoids for booster use, but not for determining the acceptability of the toxoids for use in primary immunization. Products listed in Table 1 were those recommended by the Panel on Review of Bacterial Vaccines and Toxoids With Standards of Potency for classification into Category I when used for booster immunization, and classification into Category IIIA when used for primary immunization. In addition, two immune globulins were recommended by the Panel for classification into Category IIIA (Table 2).

TABLE 1.—BACTERIAL VACCINES AND TOXOIDS RECOMMENDED FOR CLASSIFICATION IN CATEGORY I FOR BOOSTER IMMUNIZATION AND CATEGORY IIIA FOR PRIMARY IMMUNIZATION BY THE PANEL ON REVIEW OF BACTERIAL VACCINES AND TOXOIDS WITH STANDARDS OF POTENCY

Manufacturer/License Number	Product(s)
Istituto Sieroterapico Vaccinogeno Toscano (Sclavo), No. 238	Tetanus Toxoid
Lederle Laboratories, Division, American Cyanamid Co., No 17	Diphtheria and Tetanus Toxoids Adsorbed
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed
	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)
	Tetanus Toxoid
	Tetanus Toxoid Adsorbed
Merck Sharp & Dohme, Division of Merck & Co., Inc., No. 2	Tetanus Toxoid Adsorbed
Connaught Laboratories, Inc., No. 711.	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)
	Tetanus Toxoid
	Tetanus Toxoid Adsorbed
Michigan Department of Public Health, No. 99	Diphtheria and Tetanus Toxoids Adsorbed
	Tetanus Toxoid Adsorbed
Swiss Serum and Vaccine Institute Berne, No. 21	Tetanus Toxoid Adsorbed
Wyeth Laboratories, Inc., No. 3	Diphtheria and Tetanus Toxoids Adsorbed
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed
	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)
	Tetanus Toxoid
	Tetanus Toxoid Adsorbed

TABLE 2.—IMMUNE GLOBULINS RECOMMENDED FOR CLASSIFICATION IN CATEGORY IIIA FOR PASSIVE IMMUNIZATION BY THE PANEL ON REVIEW OF BACTERIAL VACCINES AND TOXOIDS WITH STANDARDS OF POTENCY

Manufacturer/License Number	Product(s)
Hollister-Stier, a Division of Cutter Laboratories, No. 8	Pertussis Immune Globulin (Human)
Travenol Laboratories Inc., Hyland Therapeutics Division, No. 140	Pertussis Immune Globulin (Human)

B. Review and Reclassification Procedures, Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency"

In the **Federal Register** of January 5, 1979 (44 FR 1544), FDA issued a final rule classifying Bacterial Vaccines and Bacterial Antigens with "no U.S. standard of potency" based on the review and recommendation of the Panel on Review of Bacterial Vaccines and Bacterial Antigens with "no U.S. Standard of Potency." In the January 1979 final rule, FDA classified the products listed in Table 3 into Category IIIA.

TABLE 3.—BACTERIAL VACCINES AND BACTERIAL ANTIGENS WITH "NO U.S. STANDARD OF POTENCY" CLASSIFIED INTO CATEGORY IIIA

Manufacturer/License Number	Product(s)
Eli Lilly and Co., No. 56	Respiratory UBA (UBA–32)[1]
Hollister-Stier, a Division of Cutter Laboratories, No. 8	Bacterial Vaccines Mixed Respiratory (MRV or MRVI; licensed as Polyvalent Bacterial Vaccines with No U.S. Standard of Potency) Bacterial Vaccines for Treatment, Special Mixtures containing only the following organisms—*Staphylococcus* (*aureus* and *albus*), *Streptococcus* (*viridans* and *nonhemolytic*), *Di plococcus pneumoniae*, *Neisseria catarrhalis*, *Klebsiella pneumoniae*, *Haemophilus influenzae* (licensed as Polyvalent Bacterial Vaccines with No U.S. Standard of Potency)
Sclavo Istituto Sieroteraico Vaccinogeno Toscano (Sclavo), No. 238	Staphylococcus Toxoid[2]
Lederle Laboratories Division, No. 17	Staphylococcus Toxoid; Formalinized: Dilution No. 1, Dilution No. 2; Digest-Modified[3]
Delmont Laboratories, Inc., No. 299	Polyvalent Bacterial Antigens with "No U.S. Standard of Potency" Staphage Lysate (SPL) Types I and III[4]

[1] Respiratory UBA, Lilly, was not reviewed by the Reclassification Committee. However, the license to manufacture this product was revoked at the request of the manufacturer on December 2, 1985. Therefore, no further regulatory action was required.
[2] The license for Staphylococcus Toxoid, Sclavo, was revoked on May 9, 1979, at the request of the manufacturer and was not, therefore, subject to reclassification.
[3] The licenses for Staphylococcus Toxoid, Lederle Laboratories, were revoked on April 3, 1979, and May 21, 1980, at the request of the manufacturer and were not, therefore, subject to reclassification.
[4] This product was originally placed in Category IIIB. However, additional data submitted by the firm were found to be adequate to reclassify the product from Category IIIB to IIIA (43 FR 50247, October 27, 1978).

C. Review and Reclassification Procedures, Skin Test Antigens

In the **Federal Register** of July 10, 1979 (44 FR 40284), FDA issued a final rule classifying skin test antigens into category IIIA based on the review and recommendations of the Panel on Review of Skin Test Antigens (hereinafter referred to as the July 1979 final rule. The July 1979 final rule placed the products listed in Table 4 into Category IIIA.

TABLE 4.—SKIN TEST ANTIGENS CLASSIFIED INTO CATEGORY IIIA

Manufacturer/License Number	Product
Michigan Department of Public Health, No. 99	Histoplasmin[1]
Hollistier-Stier, a Division of Cutter Laboratories, No. 8	Coccidioidin[2]
Iatric Corp., No. 416	Coccidioidin[3]
Massachusetts Public Health Biologic Laboratories, No. 64	Diphtheria Toxin for Schick Test[4]
Eli Lilly & Co., No. 56	Mumps Skin Test Antigen

[1] The license for Histoplasmin, Michigan Department of Public Health was revoked at the request of the manufacturer on July 30, 1979. Therefore, the product was not subject to reclassification.
[2] The license for Coccidiodin, Hollistier-Stier, was revoked at the request of the manufacturer on November 1, 1979. Therefore, the product was not subject to reclassification.
[3] Coccidiodin, Iatric, was not reviewed by the Reclassification Panel. However, the license for Coccidiodin was revoked on June 25, 1997, at the request of the manufacturer. Therefore no further regulatory action on this product is required.
[4] Diphtheria Toxin for Schick Test manufactured by Massachusetts Public Health Biologic Laboratories was reclassified from Category IIIA into Category I by FDA in a FEDERAL REGISTER publication of October 16, 1981 (46 FR 51036). This action was based on the manufacturer's completion of studies and submission of data to FDA supporting the effectiveness of the product. Accordingly, the product was not subject to reclassification.

IV. Proposed Reclassification of Category IIIA Products

In the December 1985 proposal, FDA assigned the VRBPAC, as an advisory review panel, to review all bacterial vaccines and related biological products previously classified into Category IIIA or recommended for classification into Category IIIA, and to reclassify such products into either Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded).

The VRBPAC reviewed bacterial vaccines and related biological products in Category IIIA, including those products in Category IIIA for a particular use and in Category I for another use. For example, the Committee reviewed the use of vaccines for primary immunization, but did not review their use for booster immunization in cases where they were classified in Category IIIA and Category I, respectively. The VRBPAC reviewed all Category IIIA products, that FDA assigned to it, for effectiveness only; all such products were previously found to be safe.

The VRBPAC held reclassification meetings on January 20 and 21, 1983, June 9 and 10, 1983, and September 19, 1983, and submitted a final report, dated April 1984, to FDA.

The VRBPAC's recommendations for product classifications and FDA's responses to the recommendations are discussed below.

A. Category I. (Biological Products Determined to be Safe and Effective and Not Misbranded)

Products recommended by the VRBPAC for classification into Category I for both primary and booster immunization are listed in Table 5.

TABLE 5.—PRODUCTS RECOMMENDED BY THE VRBPAC FOR CATEGORY I CLASSIFICATION FOR BOTH PRIMARY AND BOOSTER IMMUNIZATION

Manufacturer/License Number	Product(s)
Aventis Pasteur, Inc., No. 1277	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use) Tetanus Toxoid Adsorbed[1]
Lederle Laboratories Division, American Cyanamid Co., No. 17	Diphtheria and Tetanus Toxoids Adsorbed Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Tetanus and Diphtheria Toxoids Adsorbed (Adult Use) Tetanus Toxoid Tetanus Toxoid Adsorbed
Wyeth Laboratories, Inc., No. 3	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Tetanus Toxoid Adsorbed

[1] The licenses for these products were transferred from Connaught Laboratories, Inc., No. 711, to Aventis Pasteur Inc., No. 1277 on December 9, 1999.

After reviewing previously submitted data and additionally submitted data for the products listed in Table 5, the VRBPAC concluded that these products are effective for primary immunization and for booster immunization. The Committee recommended that these products be classified as Category I.

FDA agrees with the VRBPAC's conclusions and recommendations concerning the Category I classifications of the products listed in Table 5. FDA therefore proposes to designate these products as safe, effective, and not misbranded, and to accept the VRBPAC's findings.

In its final report to FDA, the VRBPAC recommended that three products be classified into Category II for primary immunization, and Category I for booster immunization. This recommendation was based on the fact that the manufacturers of these products did not submit data demonstrating the efficacy of the products for use in primary immunization. However, subsequent to the completion of the VRBPAC's review and submission of the final report to FDA, additional data were submitted to the agency in support of the efficacy of the use of these products for primary immunization. Therefore, FDA proposes to reclassify these products as safe, effective, and not misbranded for both primary and booster immunization. These products are listed in Table 6 followed by a detailed discussion.

TABLE 6.—PRODUCTS RECOMMENDED BY THE VRBPAC FOR CATEGORY II CLASSIFICATION FOR PRIMARY IMMUNIZATION AND CATEGORY I FOR BOOSTER IMMUNIZATION, WHICH FDA PROPOSES TO CLASSIFY INTO CATEGORY I FOR BOTH PRIMARY AND BOOSTER IMMUNIZATION

Manufacturer/License Number	Product(s)
Wyeth Laboratories, Inc., No. 3	Tetanus Toxoid Diphtheria and Tetanus Toxoids Absorbed
Swiss Serum and Vaccine Institute Berne, No. 21	Tetanus Toxoid Adsorbed

The VRBPAC in its initial reclassification report placed Tetanus Toxoid and Diphtheria and Tetanus Toxoids Adsorbed, manufactured by Wyeth Laboratories, Inc. (Wyeth), in Category II for primary immunization because no additional data had been submitted. However, on April 4, 1986, Wyeth submitted clinical study reports to FDA regarding the use of both Tetanus Toxoid and Diphtheria and Tetanus Toxoids Adsorbed for primary immunization. These data were reviewed by FDA and medical consultants from the VRBPAC. Both FDA and the VRBPAC consultants agreed that the clinical study data submitted by Wyeth supported reclassification of Wyeth's Tetanus Toxoid and Diphtheria and Tetanus Toxoids Adsorbed into Category I for both primary and booster immunization. Therefore, FDA proposes to designate these products as safe, effective, and not misbranded.

The VRBPAC in its initial reclassification report also placed Tetanus Toxoid Adsorbed, manufactured by Swiss Serum and Vaccine Institute Berne in Category II because no efficacy data had been submitted. However, on June 18, 1991, FDA approved a license supplement from Swiss Serum and Vaccine Institute Berne to update the firm's product license application for Tetanus Toxoid Adsorbed. The supplement included serologic data in support of primary immunization.

B. Category I for Booster Immunization and Category II for Primary Immunization. (Biological Products Determined to be Safe and Effective and Not Misbranded When Indicated for Booster Use Only)

Products recommended by the VRBPAC for classification in Category I for booster immunization and Category II for primary immunization are listed in Table 7.

TABLE 7.—PRODUCTS RECOMMENDED BY THE VRBPAC FOR CLASSIFICATION IN CATEGORY I FOR BOOSTER IMMUNIZATION AND CATEGORY II FOR PRIMARY IMMUNIZATION

Manufacturer/License Number	Product(s)
Aventis Pasteur, Inc., No. 1277	Tetanus Toxoid[1]
Merck Sharp & Dohme, Division of Merck & Co., No. 2	Tetanus Toxoid Adsorbed[2]
BioPort Corp., No. 1260	Diphtheria and Tetanus Toxoids Adsorbed[3] Tetanus Toxoid Adsorbed
Istituto Sieroterapico Vaccinogeno Toscano (Sclavo), No. 238	Tetanus Toxoid[4]

TABLE 7.—PRODUCTS RECOMMENDED BY THE VRBPAC FOR CLASSIFICATION IN CATEGORY I FOR BOOSTER IMMUNIZATION AND CATEGORY II FOR PRIMARY IMMUNIZATION—Continued

Manufacturer/License Number	Product(s)
Wyeth Laboratories, Inc., No. 3	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)

[1] The license for this product was transferred from Connaught Laboratories, Inc., No. 711, to Aventis Pasteur, Inc., No. 1277 on December 9, 1999.
[2] The license for Tetanus Toxoid Adsorbed, Merck, was revoked at the request of the manufacturer on January 31, 1986. Therefore, no further regulatory action on this product was required.
[3] The licenses for these products were transferred from Michigan Department of Public Health, No. 99, to BioPort Corp., License No. 1260 on November 12, 1998.
[4] The license for Tetanus Toxoid Vaccine, Sclavo, was revoked at the request of the manufacturer on July 27, 1993. Therefore, no further regulatory action on this product was required.

After reviewing available data, the VRBPAC recommended that the products in Table 7 be reclassified from Category IIIA to Category II for primary immunization until additional information to support effectiveness becomes available. For each of these products, either no additional information was submitted by the manufacturer or the VRBPAC found the additional information submitted was inadequate to support the effectiveness of the vaccine for primary immunization (Final Report: Addendum to Previous Panel Reports for the Reclassification of Category IIIA Biologics, April 1984).

FDA agrees with the VRBPAC's conclusions and recommendations concerning the Category II classification for primary immunization. FDA therefore proposes to designate these products as ineffective and misbranded for primary immunization and accept the VRPBAC's findings. If FDA classifies these products, under a final order, as Category II for primary immunization, it will be necessary for the agency to remove the primary immunization use from the license for each product. FDA can accomplish this if a manufacturer submits a supplement to its license that deletes the primary immunization use while maintaining the booster immunization use in the license. In order to change the license of each product in a timely manner given the required procedures of this § 601.26 reclassification process, FDA recommends that a manufacturer submit a license supplement to the agency prior to FDA publishing an NOOH on the proposed revocation of the products in Category II, which could publish as early as 30 days after the close of the comment period of this proposed order. If a manufacturer does not wish to remove the primary immunization use from its license at this time, FDA will publish an NOOH on the revocation of that use from the license after the comment period ends. In this proposed order FDA hereby offers notice of its intent to revoke the primary immunization use from the licenses of those products that have been classified as Category II for that use.

Furthermore, if a manufacturer wishes to market its product, listed in Table 7 above, for booster immunization after FDA issues a final order that classifies the product in Category II for primary immunization, the manufacturer must change its product labeling to reflect only the approved booster immunization use. Therefore, FDA is proposing that the container and package labels and the package insert include the statement "For Booster Use Only". This statement should be placed immediately following the proper name of the product and in the same size type print as the proper name. Also, any labeling references for use as a primary immunogen should be deleted. To make such a labeling revision, a manufacturer should submit a Changes Being Effected (CBE) supplement to their license in accordance with 21 CFR 601.12(c)(5) and (f)(2). FDA suggests that a manufacturer submit its labeling supplement in a timely manner so that the manufacturer may be able to market its product with appropriate labeling after a final order classifying the product in Category II for primary immunization.

C. Category II. (Biological Products Determined to be Unsafe, Ineffective or Misbranded)

The VRBPAC and the Panel on Review of Allergenic Extracts recommended that the following products listed in Table 8 be reclassified into Category II.

TABLE 8.—PRODUCTS RECOMMENDED BY THE VRBPAC AND THE PANEL ON REVIEW OF ALLERGENIC EXTRACTS FOR CATEGORY II CLASSIFICATION

Manufacturer/License Number	Product(s)
Hollister-Stier Laboratories LLC, No. 1272	Polyvalent Bacterial Vaccines with "No U.S. Standard of Potency" (Bacterial Vaccines Mixed Respiratory (MRV or MRVI, Bacterial Vaccines for Treatment, Special Mixtures)[1]
Delmont Laboratories, Inc., No. 299	Polyvalent Bacterial Antigens with "No U.S. Standard of Potency" (Staphage Lysate)
Eli Lilly and Company, No. 56	Mumps Skin Test Antigen[2]
Hollister-Stier, a Division of Cutter Laboratories, No. 8	Pertussis Immune Globulin (Human)[3]
Travenol Laboratories, Inc., Hyland Therapeutics Division, No. 140	Pertussis Immune Globulin (Human)[4]

[1] The licenses for these products were transferred from Bayer, Inc. No. 8 (formerly Hollister-Stier, a Division of Cutter Laboratories, No. 8), to Hollister-Stier, LLC, No. 1272 on June 2, 1999. These products were reviewed by the Panel on Review of Allergenic Extracts.
[2] The license for Mumps Skin Test Antigen, Lilly, was revoked on December 2, 1985, at the request of the manufacturer. Therefore no further regulatory action on this product was required.
[3] The license for Pertussis Immune Globulin, Hollistier-Stier, was revoked on August 18, 1988, at the request of the manufacturer. Therefore no further regulatory action on this product was required.
[4] The licenses for Pertussis Immune Globulin, Travenol, were revoked on April 9, 1982, and July 27, 1995, at the request of the manufacturer. Therefore no further regulatory action on this product was required.

1. Staphage Lysate

The original Panel on Review of Bacterial Vaccines and Bacterial Antigens with "no U.S. Standard of Potency," reviewed SPL manufactured by Delmont Laboratories, Inc. (Delmont). This Panel recommended that SPL be placed in Category IIIB, and that the license be revoked because: (1) There was no evidence of efficacy; and (2) if SPL was to be recommended for use as a stimulator of cell mediated immunity, either specific or general, this new "function" would require evaluation as a new biological product.

In 1978, Delmont requested a hearing in response to initiation of revocation proceedings and submitted information resulting in reclassification of SPL from Category IIIB to Category IIIA (43 FR 50247). Following this reclassification and prior to the meeting of the VRBPAC in January 1983, Delmont submitted additional information concerning SPL to the VRBPAC. This information consisted of a series of letters from physicians and patients of a testimonial nature supporting the effectiveness of SPL. These letters were accompanied by several reprints and exhibits of uncontrolled case reports and papers regarding the effectiveness and use of SPL in a variety of clinical conditions ranging from warts to hidradenitis suppurativa (HS), to chronic and progressive disorders such as multiple sclerosis (MS) and Crohn's disease.

The VRBPAC reviewed the information that Delmont submitted for the use of SPL in the treatment of the conditions described above. In addition, the VRBPAC reviewed data regarding the nonspecific stimulation of the immune response in animals. The VRBPAC noted that the information from the completed studies that were submitted indicated that the studies were insufficiently designed to support claims of SPL's effectiveness for treatment of warts, MS, Crohn's disease or nonspecific stimulation of the immune response. At the time of the VRBPAC meeting in 1983, the committee noted that two controlled trials for the use of SPL in treatment of recurrent furunculosis and HS were either in the recruitment phase or in progress. The VRBPAC noted that it would likely take additional time for the sponsors to complete these trials. However, the VRBPAC concluded that "it could not reasonably continue to defer recommendations on the classification of SPL owing to uncertainty when the two existing controlled trials would be completed, and uncertainty as to whether the results, when finally presented, would be clearly interpretable, owing to lack of comparability among patient groups" (VRPBAC Final Report: Addendum to Previous Reports for the Reclassification of Category IIIA Biologics, April 1984).

As a result of its review, the VRBPAC found that it was not able to determine that there was substantial evidence of efficacy for SPL. In its final report to the agency submitted in April of 1984, the VRBPAC recommended that SPL be placed in Category II and that "licensure be revoked until additional data to support its reclassification became available."

2. Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency"

Product licenses for Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency," (MRV, MRVI, and Bacterial Vaccines for Treatment, Special Mixtures) manufactured by Hollister-Stier, Division of Cutter Laboratories, were transferred to Miles Laboratories, Inc., on February 18, 1983, were transferred to Bayer, Inc. on May 24, 1995, and were again transferred to Hollister-Stier LLC on June 2, 1999. The original Panel on Review of Bacterial Vaccines and Antigens recommended that these products (MRV, MRVI, and Bacterial Vaccines for Treatment, Special Mixtures) be classified as Category IIIA and could remain on the market, and their license remain in effect on an interim basis provided that: (1) Group A streptococcal organisms and their derivatives, where present, were removed, and (2) satisfactory potency standards were developed and acceptable data based on scientifically sound studies which demonstrated efficacy in humans be submitted to FDA. At the time the agency established the § 601.26 reclassification panels, FDA, based on a recommendation of the VRBPAC, referred these three products to the Panel on Review of Allergenic Extracts for reclassification based on the products' attributed mode of action.

The Panel on Review of Allergenic Extracts (the Allergenics Panel) held reclassification meetings on November 19 and 20, 1982, February 18 and 19, 1983, and June 3 and 4, 1983, and a final report was submitted to FDA in December of 1983. In this report, the Allergenics Panel noted that the manufacturer had removed group A streptococcal organisms from MRV, MRVI, and Bacterial Vaccines, Special Mixtures, and had initiated preliminary studies as recommended by the original Panel. However, the Allergenics Panel found that "there has been no better definition of indications for the use of this product. Neither are there recognizable criteria for selection of patients or dosage. No double-blinded controlled studies have been performed or started since the original Panel made its recommendations in 1977" (Food and Drug Administration Panel on Review of Allergenic Extracts Category IIIA Reclassification, Final Report, December 1983). Based on the lack of efficacy studies submitted in support of these products, the Allergenics Panel recommended that these products be reclassified into Category II for both diagnosis and immunotherapy.

FDA agrees with the conclusions and recommendations of the VRBPAC to reclassify SPL into Category II. FDA therefore proposes to designate SPL as ineffective and misbranded and to accept the findings of the VRBPAC concerning SPL. FDA also agrees with the conclusions and recommendations of the Panel on Review of Allergenic Extracts to reclassify Hollister-Stier LLC's Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency" (MRV, MRVI, and Bacterial Vaccines for treatment, Special Mixtures) into Category II. FDA proposes to designate Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency" (MRV, MRVI, and Bacterial Vaccines for treatment, Special Mixtures) as ineffective and misbranded, and FDA proposes to accept the findings of the Panel on Review of Allergenic Extracts.

In this proposed order FDA hereby offers notice of its intent to revoke the licenses of SPL and Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency" (MRV, MRVI, and Bacterial Vaccines for treatment, Special Mixtures) as Category II products. After the end of the comment period for this proposed order, FDA will subsequently issue a notice of opportunity for a hearing on the revocation of the license of both SPL and Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency" (MRV, MRVI, and Bacterial Vaccines for treatment, Special Mixtures).

Section 601.26(d)(4) requires FDA to publish in a proposed order, concerning Category IIIA reclassification, a statement identifying those products that the agency proposes should be permitted to remain on the market pending further testing because there is a compelling medical need and no suitable alternative. No such products were identified by the VRBPAC for the purposes of this proposed order.

V. Availability of Reports and Public Comments

In accordance with § 601.26(d)(2), FDA is announcing the availability of the final reports of the Vaccines and Related Biological Products Advisory

Committee, dated April 1984, and the Panel on Review of Allergenic Extracts, dated December 1983, that are the subject of this proposed order. Copies of these reports can be obtained from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. By sending a self-addressed adhesive label, you will assist that office in processing your requests more quickly. The documents may also be obtained by mail by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800, or by fax by calling the FAX Information System at 1–888–CBER–FAX or 301–827–3844, or by mail by contacting CBER electronically at www.CBER_INFO@CBER.FDA.GOV.

Interested persons may, on or before August 13, 2000 submit written comments regarding this proposal to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Two copies of any comments should be submitted, except that individuals should submit one copy. Comments may also be submitted electronically at www.fda.gov/ohrms/dockets. Comments should be identified with the docket number found in brackets in the heading of this document. Data and information submitted to FDA that fall within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j) are not available for public disclosure. Consistent with the provisions of § 601.25(b), when FDA publishes this proposed order and the Reclassification Committee's reclassification findings, data and information submitted to FDA in connection with these reclassified products will be made publicly available after June 14, 2000, and may be viewed at the Dockets Management Branch (address above). Data and information submitted and shown to fall within the confidentiality provisions of one or more of the above statutes will not be disclosed. Comments concerning confidentiality should be received by FDA by June 14, 2000. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

After review of the public comments received in response to this proposed order and in consideration of the results of hearings, if any, FDA intends to issue in the **Federal Register** a final order announcing its final conclusions and revoking those licenses which are placed in Category II by the final order.

Dated: May 3, 2000.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 00–12116 Filed 5–12–00; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98E–0228]

Determination of Regulatory Review Period for Purposes of Patent Extension; Neuro Cybernetic Prosthesis (NCP®) System; Amendment

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; amendment.

SUMMARY: The Food and Drug Administration (FDA) is amending a previous determination regarding the regulatory review period for the Neuro Cybernetic Prosthesis (NCP®) System that appeared in the **Federal Register** of November 10, 1998 (63 FR 63066). FDA is amending the notice because the agency agrees with the information provided in a request from the applicant for revision of the regulatory review period (Request) (Docket No. 98E–022 8/PRC 1, dated and received on January 8, 1999).

ADDRESSES: Submit written comments and petitions to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Claudia V. Grillo, Regulatory Policy Staff (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5645.

SUPPLEMENTARY INFORMATION: In its original application for patent term extension, the applicant claimed December 16, 1991, as the date the premarket approval application (PMA) for the Neuro Cybernetic Prosthesis (NCP®) System (PMA 910070) was initially submitted. FDA first determined that the PMA was initially submitted on January 27, 1997, because FDA records indicated that the PMA submitted on December 16, 1991, had not been filed, but an amended PMA, renumbered as PMA 970003, was the PMA for the approved product.

The applicant later claimed in its request that FDA's determination of the regulatory review period failed to take into account an approved amendment to the applicant's originally submitted PMA. Therefore, the applicant requested that the agency correct the date the PMA was initially submitted to June 1, 1993, the date the approved amendment to the PMA was received by FDA.

FDA reviewed its records and confirmed that the amended PMA, received on June 1, 1993, was filed by the agency based on a threshold determination that the amended PMA was sufficiently complete to permit a substantive review. FDA later determined that additional studies were required and issued a major deficiency letter dated September 30, 1994, requesting that additional clinical studies be performed. The applicant submitted a second amendment to the PMA, which the agency received on January 27, 1997. FDA reviewed the amendment and determined that the second amendment sufficiently responded to the September 30, 1994, deficiency letter, and filed the newly amended PMA on the date of the receipt of the completed PMA, January 27, 1997. For administrative reasons, the second amendment to the PMA was considered a resubmission of the PMA, and it was assigned a new PMA number, P970003, which is the PMA number of the approved PMA for the product.

In the past, FDA has determined that the start of the approval phase began with the submission of the first filed PMA for an approved product, even if the original filed PMA was later withdrawn and filed under a new number. For this reason, FDA now accepts the date of June 1, 1993, submitted by the applicant in its request, as the date the first PMA was filed for the product and the date that the PMA was initially submitted.

Therefore, the applicable regulatory review period for the Neuro Cybernetic Prosthesis (NCP®) System is 3,237 days. Of this time, 1,730 days occurred during the testing phase of the regulatory review period, while 1,507 days occurred during the approval phase.

These periods of time were derived from the following dates, summarized from the November 10, 1998, notice and modified by this technical amendment:

1. *The date a clinical investigation involving this device was begun:* September 6, 1988.

2. *The date an application was initially submitted with respect to the device under section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e):* June 1, 1993.

3. *The date the application was approved:* July 16, 1997.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several